CLAIMS

1. A method for assembling a modulatable fusion molecule, comprising:

randomly inserting an insertion sequence into an acceptor sequence, wherein the insertion sequence and the acceptor sequence each comprise a state, thereby generating a fusion molecule; and

selecting a fusion molecule wherein insertion couples the state of the insertion sequence to the state of the acceptor sequence.

2. The method according to claim 1, wherein the state of the insertion sequence is modulated.

3. The method according to claim 2, wherein the state of the insertion sequence is modulated in response to a change in the state of the acceptor sequence.

4. The method according to claim 1, wherein the state of the acceptor sequence is modulated.

5. The method according to claim 4, wherein the state of the acceptor sequence is modulated in response to a change in the state of the insertion sequence.

6. The method according to claim 1, wherein the fusion molecule comprises a new state.

7. A method for assembling a fusion molecule comprising an insertion site, the method comprising:

inserting an insertion sequence into an acceptor sequence, thereby generating a fusion molecule, wherein the insertion sequence and the acceptor sequence each comprise a state;

generating a duplication, deletion, or substitution, at the insertion site in the acceptor sequence; and;

selecting a fusion molecule wherein insertion couples the state of the insertion sequence to the state of the acceptor sequence.

8. The method according to claim 7, wherein the generating step occurs prior to the inserting step.

9. The method according to claim 7, wherein the state of the insertion sequence is modulated.

10. The method according to claim 9, wherein state of the insertion sequence is modulated in response to a change in the activity of the acceptor sequence.

11. The method according to claim 7, wherein the state of the acceptor sequence is modulated.

12. The method according to claim 11, wherein the state of the acceptor sequence is modulated in response to a change in the state of the insertion sequence.

13. The method according to claim 7, wherein the fusion molecule comprises a new state.

14. A method for assembling a multistable fusion molecule which can switch between at least an active state and a less active state, comprising:

randomly inserting an insertion sequence into an acceptor sequence, thereby generating a fusion molecule, wherein either the insertion sequence or the acceptor sequence comprises a state; and wherein the respective other sequence is responsive to a signal;

selecting a fusion molecule, wherein the state is coupled to the signal, such that the fusion molecule switches state in response to the signal.

15. A method for assembling a fusion molecule, comprising:

randomly inserting an insertion sequence responsive to a signal into an acceptor sequence comprising a state, thereby generating a fusion molecule; selecting for a fusion molecule wherein the state of the acceptor sequence is responsive to the signal.

16. The method according to any of claims 1, 7, 14, and 15, wherein said insertion sequence and acceptor sequence comprise polypeptides.

17. The method according to claim 16, wherein said inserting comprises obtaining a first nucleic acid fragment encoding said insertion polypeptide and a second nucleic acid fragment encoding said acceptor polypeptide and randomly

inserting said first nucleic acid fragment into said second nucleic acid fragment.

18. The method according to claim 17, further comprising the step of digesting the second nucleic acid fragment with a nuclease.

19. The method according to claim 17, comprising the step of generating random fragments of nucleic acid sequences and inserting a fragment at random into a nucleic acid encoding the acceptor sequence.

20. The method according to claim 17, wherein the step of generating random fragments comprises exposing a nucleic acid sequence encoding the acceptor sequence to a nuclease, mechanically shearing the nucleic acid, exposing the nucleic acid to a chemical, and/or exposing the nucleic acid sequence to radiation.

21. The method according to claim 20, wherein the nuclease is selected from the group consisting of one or more of: DNAse I, S1 nuclease, mung bean nuclease, and a restriction endonuclease.

22. The method according to claim 17, further comprising the step of randomly inserting first nucleic acid fragments into second nucleic acid fragments, a plurality of times sequentially or simultaneously.

23. The method according to claim 1, further comprising providing a library of acceptor polypeptides comprising randomly inserted insertion polypeptide sequences, and selecting fusion polypeptides wherein the states of the insertion and acceptor polypeptides are coupled.

24. The method according to claim 22, wherein the step of inserting a plurality of times generates a library of nucleic acid molecules expressing fusion polypeptides comprising acceptor polypeptides which comprise randomly inserted insertion polypeptide sequences.

25. The method according to claim 22, further comprising selecting fusion polypeptides in which the state of the insertion polypeptide sequence is coupled to the state of the acceptor polypeptide sequence.

26. A method for modulating a cellular activity, comprising:

providing a fusion molecule generated according to the method of any of claims 1, 7, 14, and 15 to a cell, wherein a change in state of at least the insertion sequence or the acceptor sequence modulates a cellular activity, and wherein the change in state which modulates the cellular activity is coupled to a change in state of the respective other portion of the fusion molecule; and

changing the state of the respective other portion of the fusion molecule, thereby modulating the cellular activity.

27. A method for delivering a bio-effective molecule to a cell, comprising:

providing a fusion molecule associated with a bio-effective molecule to the cell, the fusion molecule comprising an insertion sequence and an acceptor sequence, wherein either the insertion sequence or the acceptor sequence binds to a cellular marker of a pathological condition and wherein upon binding to the marker, the fusion molecule dissociates from the bio-effective molecule, thereby delivering the molecule to the cell.

28. A method for delivering a bio-effective molecule intracellularly, comprising:

providing a fusion molecule associated with a bio-effective molecule to the cell, the fusion molecule comprising an insertion sequence and an acceptor sequence,

wherein either the insertion sequence or acceptor sequence comprises a transport sequence for transporting the fusion molecule intracellularly, and

wherein release of the bio-effective molecule from the fusion molecule is coupled to transport of the fusion molecule intracellularly.

29. The method according to claim 28, wherein either the insertion sequence or the acceptor sequence is capable of binding to a biomolecule, and wherein binding the fusion molecule with the biomolecule localizes the fusion molecule comprising the bio-effective molecule intracellularly and disassociates the bio-effective molecule from the fusion molecule.

30. A method for modulating a molecular pathway in a cell, comprising:

providing a fusion molecule to the cell, the fusion molecule comprising an insertion sequence and an acceptor sequence,

wherein the activity of the insertion sequence and acceptor sequence are coupled, and responsive to a signal, and

wherein the activity of either the insertion sequence or the acceptor sequence modulates the activity or expression of a molecular pathway molecule in the cell; and

exposing the fusion molecule to the signal.

31. A method for controlling the activity of a nucleic acid regulatory sequence, comprising:

providing a fusion molecule, the fusion molecule comprising an insertion sequence and an acceptor sequence,

wherein either the insertion sequence or the acceptor sequence responds to a signal, and

wherein the respective other sequence of the fusion molecule binds to the nucleic acid regulatory sequence when the signal is responded to; and

exposing the fusion molecule to the signal.

32. A fusion molecule, comprising:

an insertion sequence and an acceptor sequence,

wherein either the insertion sequence or the acceptor sequence transports the fusion molecule intracellularly and wherein intracellular transport of the fusion molecule is coupled to binding of the fusion molecule to a bio-effective molecule.

33. A fusion molecule, comprising:

an insertion sequence and an acceptor sequence, wherein either the insertion sequence or the acceptor sequence binds to a nucleic acid molecule, and wherein nucleic acid binding activity is coupled to the response of the respective other sequence of the fusion molecule to a signal.

34. A fusion molecule, comprising:

an insertion sequence and an acceptor sequence, wherein either the insertion sequence or the acceptor sequence associates with a bio-effective molecule, and disassociates from the bio-effective molecule, when the

respective other sequence of the fusion binds to a cellular marker of a pathological condition.

35. A fusion molecule capable of switching from a non-toxic to a toxic state, comprising:

an insertion sequence and an acceptor sequence, wherein either the insertion sequence or acceptor sequence binds to a cellular marker of a pathology, and wherein binding of the marker to the fusion protein switches the fusion protein from a non-toxic state to a toxic state.

36. A fusion molecule capable of switching from a toxic state to a less toxic state, comprising:

an insertion sequence and an acceptor sequence, wherein either the insertion sequence or acceptor sequence binds to a cellular marker of a healthy cell, and wherein binding of the marker to the fusion protein switches the fusion protein from a toxic state to a less toxic state.

37. A molecular switch for controlling a cellular pathway, comprising:

a fusion molecule comprising an insertion sequence and an acceptor sequence,

wherein the state of the insertion and acceptor sequence are coupled, and responsive to a signal, and

wherein the state of either the insertion sequence or the acceptor sequence modulates the activity or expression of a molecular pathway molecule in a cell.

38. A sensor molecule, comprising:

an insertion sequence and an acceptor sequence,

wherein either the insertion sequence or acceptor sequence binds to a target molecule,

wherein the respective other sequence generates a signal in response to binding, and further,

wherein the acceptor sequence comprises a deletion, duplication, and or substitution at the insertion site.

39. A library, comprising a plurality of library members,

wherein each library member comprises a first nucleic acid sequence encoding a first polypeptide having a first state, the first nucleic acid sequence being inserted into a second nucleic acid sequence encoding a second polypeptide having a second state, at a random insertion site in the second nucleic acid sequence, and wherein the library comprises members comprising insertions with deletions at the insertion site, insertions with tandem duplications at the insertion site, and insertions with neither duplications nor deletions.

40. A library comprising a plurality of library members comprising fusion molecules generated according to any of claims 1, 7, 14, or 15.

41. A method for generating a conditional heterodimer, comprising:

providing a plurality of randomly bisected molecules;

each bisected molecule comprising a first half and a second half, wherein the first and second half are fused to first and second dimerization domains respectively, and wherein a function of the bisected molecule is altered by bisection,

selecting for restoration of function of a bisected molecule in response to a signal.

42. A method for modulating a cellular activity comprising: providing a conditional heterodimer obtained by the method of claim 41 to a cell that lacks the function of the molecule.

43. The method according to claim 42, further comprising: exposing the cell to the signal.

44. The method according to claim 43, wherein the signal comprises the presence, absence or level of a CID molecule.